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Award Number: DAMD17-02-1-0558

TITLE: Statistical Inference for Quality-Adjusted Survival Time

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REPORT DATE: August 2003

TYPE OF REPORT: Annual Summary

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	August 2003	Annual Summary (15 Jul 02-14 Jul 03)

4. TITLE AND SUBTITLE
Statistical Inference for Quality-Adjusted Survival Time

5. FUNDING NUMBERS
DAMD17-02-1-0558

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT (Maximum 200 Words)

In evaluations of breast cancer therapies, the patients' quality of life is receiving more and more attention. It is desirable that a treatment not only prolongs the overall survival life, but also improves the quality of life (QOL). Quality-adjusted lifetime (QAL) is a measure that combines both the quality and the quantity of a person's lifetime. The goal of my research is to study how to draw inference about QAL in the presence of censoring. For the past year, I have made efforts to ensure that the methodology I develop can be easily applied to clinical study of breast cancer. I have also been attacking some difficult technical problems. I am confident that the research problem I have been working on is of great importance to breast cancer studies.

14. SUBJECT TERMS
Quality of life, censored data, survival analysis

15. NUMBER OF PAGES
8

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

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Annual Summary Report

Statistical Inference for Quality-Adjusted Survival Time

Hongwei Zhao, Sc.D

a. Introduction

In evaluations of breast cancer therapies, the patients' quality of life is receiving more and more attention. It is desirable that a treatment not only prolongs the overall survival life, but also improves the quality of life (QOL). Quality-adjusted lifetime (QAL) is a measure that combines both the quality and the quantity of a person's lifetime. First proposed by Gelber, Gelman and Goldhirsch (1989), QAL is simply an integration of survival time weighted by a utility coefficient ranging from 0 (poor health) to 1 (perfect health). In a typical clinical trial setting, patients are enrolled over time, and the study ends before observation of the endpoints for all patients. Therefore, the data are right censored. The goal of my research is to study how to draw inference about QAL in the presence of censoring.

b. Body

Thanks to the support of my research time for the past year from this grant, I was able to concentrate on developing methodologies for analyzing quality-adjusted lifetime and other statistical problems encountered in breast cancer research. I have been working closely with breast cancer quality of life specialists in the hope of making my method more relevant to breast cancer clinical studies. I also spent a lot of time studying the general representation theory for missing data developed by Robins and Rotnitzky (1992), and Robins, Rotnitzky and Zhao (1994), which will be used heavily for drawing inference for QAL. I believe these time were well spent since (1) it is crucial that any results I obtain can be applied to breast cancer studies in a practical setting; and (2) a good grasp of the foundation of theory will facilitate new methodology development.

The tasks for this past year which were proposed in the Statement of Work of my grant were: (1) To develop efficient, consistent estimators for the survival functions of quality-adjusted lifetime; (2) To develop efficient test procedures for comparing the equality of two survival functions of quality-adjusted lifetime. I have not followed exactly the statement of work and here are the reasons for some of the deviations. In my original grant, I made the assumption that utility coefficients for quality of life measures were either known or can be pre-specified. However, in a real breast cancer clinical trial setting, the QOL questionnaires are collected periodically, and they often range from 1 to some integer, 50, for example. Missing items from a questionnaire

and missing questionnaires often occur. It remains a problem how to use these data to determine the utility coefficients which are on a scale from 0 to 1. I tried to address this problem before carrying out the tasks outlined in my original grant. My research work for the past year can be summarized as follows:

i. Determining utility coefficients from QOL questionnaires

For each study, every effort should be made to encourage and facilitate patients' completion of questionnaires. However, no matter how good the design of a study is, missing data often occur. In the event that missing data occur, it is important to collect information on why the data are missing. According to Little and Rubin (1987), missing data can be classified as missing completely at random (MCAR), missing at random (MAR), missing not at random (MNAR). If it is reasonable to assume MCAR or MAR, then the multiple imputation methods (Little and Yau, 1996) can be used for missing items from a questionnaire or missing questionnaires. The analysis will become more complicated if the missing is non-ignorable, or MNAR. We need to assume a model for the mechanism of missing data and the validity of our result will depend on whether the model we have assumed for the missing data is correct.

Quality of life measures usually take values on a scale from 1 to some positive integer, for example, 50, and they vary from one person to another. If we simply choose some function and convert each person's QOL to a utility coefficient ranging from 0 to 1 (for example, rescaling), then treatment comparison will depend highly on each person's own perception of QOL. In general, we do not wish that our recommendation of treatment is highly influenced by individual data. Hence, I propose performing ANOVA analysis, and obtaining a mean QOL score at each data collection point, for each treatment group. The mean QOL scores are then transformed to mean utility coefficients on a scale of 0 to 1. I am in the process of applying this methodology to a real data set.

ii. Estimating survival functions of quality-adjusted lifetime

Zhao and Tsiatis (1997, 1999) outlined the form for the most efficient estimator for the survival function of QAL. Since the efficient estimator depends on some functional of health history process, it cannot be estimated non-parametrically. Instead, Zhao and Tsiatis (1999) proposed some ways of improving the so-called simple weighted estimators. So far I have not been able to find any estimators that can improve consistently upon the estimators proposed by Zhao and Tsiatis (1999).

iii. Testing equality of survival functions of quality-adjusted lifetime

We mainly consider the inverse probability weighting technique for developing test statistics for equality of survival functions of QAL. If an influence function for a test statistic exists for complete data case, denoted as ψ_i, then a test statistic for censored

case can be constructed as

$$n^{-1}\sum_{i=1}^{n}\frac{\Delta_i\psi_i}{\widehat{K}(T_i)},$$

where Δ_i is an indicator whether the subject i's death is observed, and $\widehat{K}(T_i)$ is an estimator for the survival function for the censoring variable.

Zhao and Tsiatis (2001) proposed a test statistic where ψ_i is the influence function of the general logrank test:

$$\psi_i = \int_0^\infty w(u)\left[Z_i - \frac{E\{Z_i I(Q_i \geq u)\}}{E\{I(Q_i \geq u)\}}\right] dM_i^Q(u),$$

where Z_i is the treatment indicator, Q_i is the quality adjusted survival time for subject i, $w(u)$ is any weighting function, $M_i^Q(u) = I(Q_i \leq u) - \int_0^u \lambda^Q(t)I(Q_i \geq t)dt$, $\lambda^Q(t)$ is the hazard function for Q_i, which under the null hypothesis is independent of Z_i. They showed that by choosing a certain weight $w(u)$, the test statistic became the ordinary logrank test when the utility coefficient is equal to 1 everywhere until a subject's death.

We have considered other forms of test statistics. One option is to use an influence function ψ_i that is generated by alternative hypothesis of accelerated life time model. Another option is to use Pepe and Fleming (1989) test with censored data, where the survival function for each treatment can be estimated consistently using methods of Zhao and Tsiatis (1997). Simulation study is under way to determine which test statistic is more powerful under different alternative hypotheses.

c. Key Research Accomplishments

1. I have determined how to obtain the utility coefficients for quality adjusted survival time.

2. I have a better understanding of the general representation theory for missing data process.

3. I have worked on ways of improving test statistics for equality of survival functions of QAL.

d. Reportable outcomes

Invited speaker for the Joint Statistical Meetings, August 3-7, 2003, San Francisco, CA. My talk was titled "Statistical Inference for Quality-Adjusted Survival Time".

e. Conclusions

I believe the research problem I have been working on is of great importance to breast cancer studies. For the past year I have made efforts to ensure that the methodology I develop can be easily applied to clinical study of breast cancer. I have also been attacking some difficult technical problems. I am confident that I will obtain some good results by the end of the grant period.

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